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ORIGINAL ARTICLE

Maternal and neonatal outcomes after antenatal corticosteroid administration for PPROM at 32 to 33 6/7 weeks gestational age*

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Abstract

Background: Preterm Premature Rupture of Membranes (PPROM) precedes many deliveries and experts agree with expectant management until 34 weeks gestation. However, there is controversy regarding the gestational age (GA) for administration of corticosteroids.

Study design: We performed a retrospective cohort study in the University of California Fetal Consortium (UCfC). We searched available charts of singleton pregnancies with PPROM between 32 and 33 6/7 weeks GA. Outcomes from the groups were analyzed.

Results: Of 191 women with PPROM at 32 to 33 6/7 weeks, 150 received corticosteroids. The median GA at admission was earlier for the exposed versus unexposed group (32 4/7 versus 33 0/7 weeks, respectively, $p = 0.001$). The mean GA at delivery in the exposed was 33 2/7 (32 0/7 to 35 0/7) weeks versus 33 5/7 (32 0/7 to 36 1/7) weeks in the unexposed ($p = 0.001$). There was no difference in chorioamnionitis or RDS.

Conclusion: In women with PPROM at 32 to 33 6/7 weeks, our data suggests that corticosteroids are associated with similar outcomes despite earlier GA at delivery and no differences in major morbidities. A larger prospective study is needed to determine if the benefit of corticosteroids outweighs the potential risks in PPROM.

Keywords

Preterm premature rupture of membranes, corticosteroids, prematurity, neonatal sepsis, chorioamnionitis, fetal membranes

History

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Introduction

Antenatal corticosteroids are an important intervention to improve neonatal outcomes after preterm birth, including those resulting from preterm premature rupture of membranes (PPROM). Treatment with corticosteroids is associated with significant reductions in rates of RDS, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and overall reductions in neonatal death [1–4]. However, in cases of PPROM at 32 to 33 6/7 weeks, there has been controversy about the use of antenatal corticosteroids and various recommendations have been made about optimal management in this specific gestational age window.

An ACOG Committee Opinion from 2011 states that the efficacy of corticosteroid use at 32 to 33 completed weeks of gestation for PPROM is unclear, but that treatment may be beneficial, particularly if pulmonary immaturity is documented [5]. Subsequently, the most recent ACOG Practice Bulletin on

PPROM recommends corticosteroids from 24 to 33 6/7 weeks gestation unless fetal lung maturity is documented [6]. An interim update to this Practice Bulletin, states that a single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 34 0/7 weeks of gestation [7].

The use of antenatal corticosteroids in PPROM has been evaluated in numerous trials and shown to reduce neonatal mortality, RDS, IVH, and NEC [7–9]. We agree that corticosteroids have been shown to be beneficial regardless of membrane status, however the data for corticosteroids in setting of gestational age > 32 weeks is insufficient. The data on which the newest recommendation is made are limited for the gestational ages after 32 completed weeks.

Objective

In order to address this ambiguity, we performed a retrospective observational study to evaluate whether exposure to a single course of antenatal corticosteroids between 32 and 33 6/7 weeks gestational age in PPROM was associated with a difference in maternal and neonatal outcomes.

Material and methods

We performed a retrospective analysis of women with singleton pregnancies who were diagnosed with PPROM at

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32 to 33 6/7 weeks gestation from the five University of California (UC) campuses. Multi-institutional review board reliance registry approval was obtained for the study. We reviewed records from each of the UC campuses (2004–2013) using the ICD-9 code for PPROM, including associated modifiers. These cases were further filtered by careful hand reviewing of the charts to identify only cases of PPROM occurring between 32 and 33 6/7 weeks. Inclusion criteria included singleton pregnancies in women admitted to one of the five UC Medical Centers with a diagnosis of PPROM. Exclusion criteria included a diagnosis of clinical chorioamnionitis on admission, previous exposure to antenatal corticosteroids, nonreassuring fetal heart rate pattern on admission, cerclage, fetus with growth restriction less than 10th percentile, or fetus with congenital anomaly.

We stratified the cases into two groups according to antenatal corticosteroid exposure. Data were collected regarding administration of antibiotics, latency interval, gestational age at delivery, and maternal/intrapartum morbidities, including preeclampsia, abruption, chorioamnionitis, and postpartum hemorrhage. Neonatal data collected included birthweight, incidence of respiratory distress syndrome, and NICU length of stay.

We used Chi-square test, Student *t*-test, and Mann-Whitney *U* test where appropriate. The results are presented as median with ranges. Statistical analyses were performed using SPSS 20.0 (IBM Corp., Armonk, NY) with *p* values <0.05 considered to be statistically significant.

Results

Our final identified cohort included 191 women with singleton pregnancies and PPROM at 32 to 33 6/7 weeks gestational age. Of these women, 150 received corticosteroids and 41 did not (Figure 1). Baseline maternal characteristics for these women are presented in Table 1. With the exception of the gestational age at admission, maternal and obstetrical characteristics were similar in the two groups. For those who

received corticosteroids, the gestational age at admission was earlier than the non-administration group (32 4/7 versus 33 0/7 weeks, respectively, $p=0.001$). Another difference seen in our analysis was a higher rate of GBS negative evaluations. We note that the majority of cases were “GBS unknown”, with a higher rate of GBS unknown in the corticosteroid unexposed group.

Maternal and neonatal outcomes are presented in Table 2. There was no difference in the incidence of either chorioamnionitis or RDS between the two groups; this persisted even after adjusting for gestational age at admission and delivery. The incidence of chorioamnionitis was similar in the corticosteroid exposed and unexposed groups (chorioamnionitis: 12.8 versus 10%, respectively, $p=0.43$; endometritis: 2.5 versus 2.7%, $p=0.66$). There was no difference in the length of NICU stay between the exposed and unexposed groups.

Discussion

PPROM complicates approximately 3% of all singleton pregnancies in the US [8,9], is an inciting factor in about one third of all preterm deliveries, and is associated with significant perinatal morbidity and mortality [10–12]. Most agree with expectant management between ~24 and ~34 weeks gestation [6]. Administration of antenatal corticosteroids is considered an important adjunct to minimize neonatal mortality and morbidity [13] and is recommended for all women at threat for preterm delivery from 24 to 33 6/7 weeks gestation unless fetal lungs are mature. This now includes women with PPROM [6].

The history regarding corticosteroids in setting of PPROM has evolved greatly over the last few decades. In 1994, a National Institute of Health (NIH) consensus panel released its first statement regarding corticosteroid administration to women in preterm labor, recommending the use of corticosteroids in PPROM from 24 to 32 weeks gestation [2]. This statement cautioned against indiscriminate corticosteroid use in PPROM and recommended against use after 32 weeks

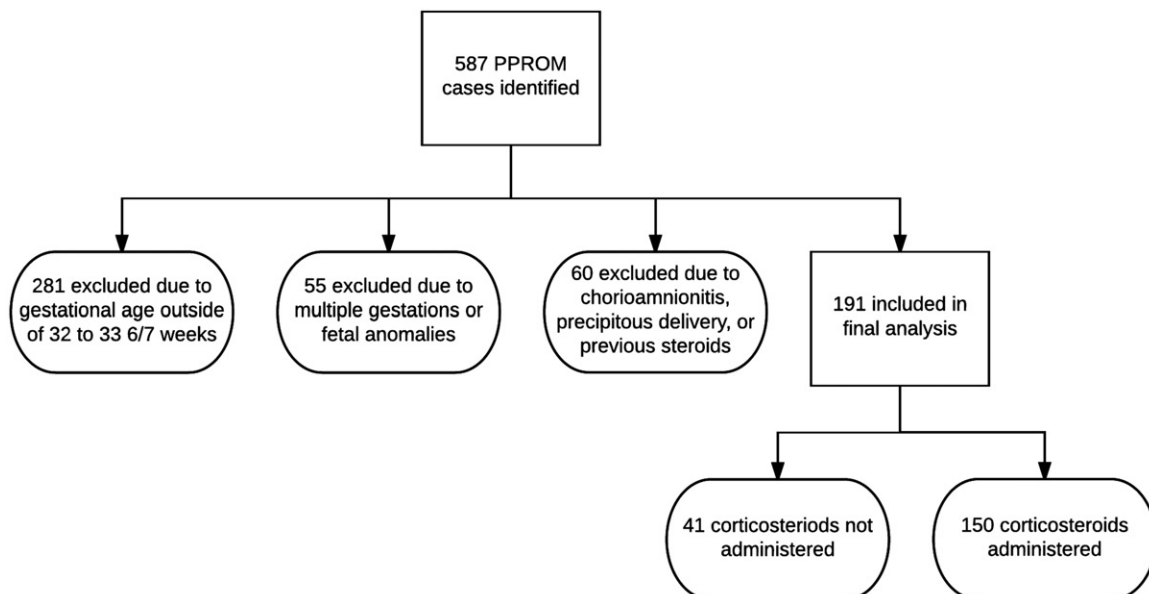


Figure 1. Flowchart of identified PPROM cases.

Table 1. Maternal characteristics for women receiving none or a single corticosteroid course.

Characteristics	Corticosteroids not administered, <i>N</i> = 41	Corticosteroids administered, <i>N</i> = 150	<i>p</i> values
Age (years)	28 (16–47)	29 (15–54)	0.40
Parity			0.51
0	25 (61%)	77 (51%)	
1–3	15 (36.6%)	66 (44.0%)	
>3	1 (2.4%)	7 (4.7%)	
BMI (kg/m ²)	28 (20–40)	26 (17–50)	0.26
Race			0.37
Hispanic	20/38 (52.6%)	49/133 (36.8%)	
Caucasian	14/38 (36.8%)	48/133 (36.1%)	
Black	1/38 (2.6%)	10/133 (7.5%)	
Nat American	0 (0%)	2/133 (1.5%)	
Asian	1/38 (2.6%)	9/133 (6.8%)	
Other/Unknown	2/38 (5.3%)	15/133 (11.3%)	
GA at admission	33 0/7 (32 0/7–33 6/7)	32 4/7 (31 6/7–33/67)	0.001
Pregestational Diabetes Type 1	1 (2.4%)	2/145 (1.4%)	0.52
Pregestational Diabetes Type 2	3 (7.3%)	9/137 (6.2%)	0.51
GDM	5 (12.2%)	21/145 (14.5%)	0.71
Hypertension	1/21 (4.8%)	8/109 (7.3%)	0.56
Chronic hypertension	4/40 (100%)	8/136 (5.9%)	0.28
Previous cesarean	4/12 (33.3%)	15/97 (15.5%)	0.12
GBS Carrier			0.02
No	5/40 (12.5%)	48/137 (35.0%)	
Yes	6/40 (15.0%)	13/137 (9.5%)	
Unknown	29/40 (72.5%)	76/137 (55.5%)	

Abbreviations: BMI: body mass index; GA: gestational age; GDM: gestational diabetes mellitus; GBS: group B streptococcus.

Significance calculated via Chi-square, Fisher's exact *t*-test, Mann–Whitney *U* test. Kurtosis of ± 2 11 distribution.

Data presented as *n* (%), median (range).

Table 2. Maternal and neonatal outcomes.

Outcome	Corticosteroids not administered (<i>n</i> = 41)	Corticosteroids administered (<i>n</i> = 150)	Unadjusted odds ratio (95% confidence interval)	<i>p</i> values
GA at delivery	33 5/7 (32 0/7–36 1/7)	33 2/7 (32 0/7–35 0/7)	–	0.001
Latency period (days)	1 (0–18)	2 (0–21)	–	0.77
Birthweight (g)	2,210 (1,010–3,050)	2,060 (1,250–3,120)	–	0.08
Newborn female sex	22 (53.7%)	60 (40.3%)	0.58 (0.29–1.17)	0.13
5-minute Apgar <5	2/41 (4.9%)	6/144 (4.2%)	–	0.56
Respiratory distress syndrome (RDS)	15/39 (38.5%)	49/146 (33.6%)	0.81 (0.39–1.68)	0.57
NICU length of stay (days)	18 (0–114)	15 (0–134)	–	0.28
NICU stay (>34 days)*	7/40 (17.5%)	9/136 (6.6%)	0.33 (0.12–0.96)	0.04
IUGR	1/21 (4.8%)	3/109 (2.8%)	0.57 (0.06–5.72)	0.51
Preeclampsia	3/21 (14.3%)	12/109 (11.0%)	0.74 (0.19–2.90)	0.45
Chorioamnionitis	4/40 (10.0%)	19/148 (12.8%)	1.33 (0.42–4.14)	0.43
Endometritis	1/37 (2.7%)	3/121 (2.5%)	0.92 (0.09–9.07)	0.69
Placental abruption	1/21 (4.8%)	6/109 (5.5%)	1.16 (0.13–10.21)	0.66
Cesarean delivery	15 (36.6%)	48 (32.2%)	0.82 (0.40–1.70)	0.60
Retained placenta	0/21 (0%)	1/109 (0.9%)	–	–

Abbreviations: GA: gestational age; IUGR: intrauterine growth restriction; NICU: neonatal intensive care unit.

Expressed as mean (standard deviation) or median (range). Significance calculated via Chi-square, Fisher's exact, Student *t*-test, Mann–Whitney *U* test.

Kurtosis of ± 2 used for determining normality of distribution.*>34 days analyzed as this was average NICU stay in previous study of PPRM at 33 weeks [29].

gestation due to concerns for infection [2]. These recommendations were seconded by the Society of Obstetricians and Gynaecologists of Canada (SOGC) in 1995 [14] and an ACOG Committee Opinion in 1998 [15].

In 2000, NIH convened another Consensus Panel to address this topic. In an updated statement, the panel recommended that *all* women between 24 and 34 weeks gestation who are at risk of preterm delivery within seven days should be considered candidates for a single course of corticosteroids [16]. However, it did not specifically address PPRM at 32–34 weeks. The SOGC updated statement in 2003 reads, “women at risk of preterm delivery within 7 days

should be considered candidates for antenatal treatment with a single course of corticosteroids” [17], but also does not specify gestational age thresholds for steroid administration with PPRM.

A recent randomized controlled trial has concluded that administration of betamethasone to women at risk for late preterm delivery significantly reduces the rate of neonatal respiratory complications in pregnancy at 34 to 36 6/7 weeks [18]. In this study approximately 22% of subjects in each group (Betamethasone versus placebo) had ruptured membranes as the indication for trial entry. They did not find a significant between-group difference in the rates of maternal

or neonatal infectious complications [18]. However, the study was not powered specifically to address use of corticosteroids in setting of ruptured membranes.

The establishment of the upper limits of GA for corticosteroid administration in the face of PPROM is controversial [4,19,20], as there are few data that attest to the risk/benefit ratio of corticosteroid administration for PPROM after 32 weeks gestation. Some believe that at this gestational age, there is an increased risk of maternal immunocompromise, chorioamnionitis/endometritis, and neonatal sepsis with administration of corticosteroids [21,22], and these risks surpass the potential benefits of corticosteroids in decreasing the risks of neonatal morbidities such as RDS [23–26]. However, at the time many of the earlier studies were conducted, the practice of administration of latency antibiotics for PPROM had not yet been adapted.

A more recent Cochrane systematic review concludes that corticosteroids should be administered up to 34 weeks. In this newer review, antenatal corticosteroids are shown to be beneficial in the subgroup of infants whose mothers have PPROM. However, many of the 21 studies that were included in this systematic review were focused on subjects with a gestational age range less than 32 weeks [4].

In our cohort study, we observed that the incidence of chorioamnionitis and RDS were not statistically significant between the corticosteroid exposed and unexposed groups in cases of PPROM between 32 to 33 6/7 weeks gestational age. There NICU length of stay was similar between the two groups and there were no differences in major neonatal morbidities. Prolonged NICU course was chosen as an outcome measure because the NICU length of stay imposes both emotional and economic burdens on the family and society as well as contributes to increased neonatal morbidity due to nosocomial infections [27,28].

The main strength of our study is that it specifically addresses this very precise gestational age window of 32 to 33 6/7 weeks. Another strength is that the data were collected from all five UC medical campuses, representing a racially and ethnically diverse population distributed over a wide geographical area. Thus, the external validity of the results is considered high.

We acknowledge that there are several limitations to this study. The data were collected from multiple institutions with varying definitions for clinical outcomes such as chorioamnionitis and RDS. Additionally, each of the institutions and individual physicians at the institutions adhered to their own policies regarding management of subjects with PPROM resulting in variability of type and duration of latency antibiotic treatment and decision to administer corticosteroids. Also, although we excluded the cases that delivered precipitously, we did not have information on the cervical exam at the time of admission, this could have influenced the practitioners' decisions regarding corticosteroid administration. Furthermore, ICD-9 codes were utilized to initially identify cases of PPROM; poor coding and database management could have lead to failure in identifying all available cases. Finally, we did not have information on the specific type of corticosteroid administered and the number of doses given per steroid course, and therefore could not adjust for these variables in our analysis.

Given the lack of data in this specific gestational age window, we conclude that an adequately powered prospective randomized controlled trial is needed to rigorously determine the relative risks and benefits of corticosteroid administration in patients affected by PPROM occurring after 32 weeks gestational age, and that clinical equipoise exists in this area, justifying the performance of such a study.

Declaration of interest

The authors report no conflict(s) of interest.

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